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TITLE: **Rapamycin** impairs antigen uptake of human **dendritic** cells.
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AB BACKGROUND: **Rapamycin** is a recently introduced immunosuppressive agent. Its effect on lymphocytes has been extensively studied. Whether it can also modulate **dendritic** cell (DC) function is unknown. METHODS: The effect of **rapamycin** on differentiation, antigen uptake, and the immunostimulatory capacity of human DC was examined. DC were derived from monocytes upon culture with interleukin (IL)-4 and granulocyte-macrophage colony-stimulating factor in the presence or absence of **rapamycin** (0.1-100 ng/mL). Surface phenotype and antigen uptake capacity of DC were assessed by flow cytometry. Immunostimulatory capacity was measured by mixed lymphocyte culture. RESULTS: **Rapamycin** reduced DC recovery and increased DC apoptosis. DC differentiated in the presence of **rapamycin** (rapa-DC) had increased expression of CD1a, CD1b, and CD1c and decreased expression of MHC I, MHC II, CD80, CD86, and CD40. Antigen uptake receptor expression (mannose receptor, CD32, CD91, CD46) was decreased, and receptor-mediated endocytosis of fluorescein isothiocyanate-dextran was markedly impaired in rapa-DC, as were fluid phase endocytosis of Lucipher Yellow and phagocytic activity of bacteria and dead or apoptotic cells. CD40 ligand-induced production of both IL-12 and IL-10 was reduced in rapa-DC, and allogeneic T lymphocyte responses were moderately impaired when rapa-DC were used as stimulator cells. Neither cyclosporine nor FK506 affected DC function. However, the effects of **rapamycin** on DC could be completely inhibited by a 10-fold excess of FK506 but not by up to 100-fold excess of cyclosporine. CONCLUSION: **Rapamycin** has a unique and profound inhibitory effect on DC function, which seems to be at least in part mediated by the FKBP immunophilins.